REMARKS

I. Status of the Claims

With this response, claims 2-14, 16, 42-46, 51 and 52 are canceled, and claims 1 and 15 are amended without prejudice or disclaimer. Claims 1, 15, 17-41 and 47-50 remain pending.

II. Election/Restriction

In response to the Office action mailed on June 16, 2010, applicants elected Group IX and the compound of formula (I) wherein m and n are each 0, and R^1 and R^2 are each $-CH_2CF_3$. At least claims 1, 15-16, 43 and 49-50 read on the elected species. Applicants reserve the right to pursue the non-elected subject matter in one or more divisional application(s).

III. Claim Objections

The Office has objected to claims 15-16 for the following informalities: "the claims recite 'each R1' in the first lines; however, there is only one R1 recited in the compound of claim 1…"

Solely to advance prosecution, applicants have canceled claim 16 and amended claim 15, as well as claim 1, to remove the word "each". The proposed amendments are believed to obviate this objection.

Accordingly, applicants respectfully request withdrawal of this objection.

IV. Claim Rejections - 35 U.S.C. § 112, ¶ 2

The Office has rejected claims 1, 15-16 and 43 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention. The Office action states:

> Claim 1 recites a compound of formula (I); however, the depicted formula (I) has a net charge of -1, i.e., formula (I) depicts an ion. Since compounds normally are comprised of molecules that have a neutral charge, the subject matter of the recited 'compound of formula (I)' is confusing.

(Office action, page 3).

Solely to advance prosecution, applicants have amended claim 1 to recite: "A compound comprising a zwitterion of formula (I)…" The proposed amendment is believed to obviate this rejection.

Accordingly, applicants respectfully request withdrawal of this rejection.

V. Claim Rejections - 35 U.S.C. § 112, ¶ 1 - Written Description

The Office has rejected claim 1 as failing to comply with the written description requirement. The Office action states:

> The generic terms recited in the instant claims of "hydrates" and "solvates" of the compounds of formula (I) and of the elected compound are not considered to have sufficient description in the specification to demonstrate applicant was in possession at the time of filing of each of these genus terms with respect to the elected compound.

(Office action, pages 3-4).

Solely to advance prosecution, applicants have deleted the terms "hydrate" and "solvate" from claim 1. The proposed amendments are believed to obviate this rejection.

Accordingly, applicants respectfully request withdrawal of this rejection.

VI. Claim Rejections - 35 U.S.C. § 112, ¶ 1 - Enablement

The Office has rejected claim 1 for lack of enablement. The Office action states:

> [W]hile being enabling for how to make some compounds of formula (I), [the specification] does not reasonably provide enablement for how to make "solvates" or "hydrates" of the elected compound.

(Office action, page 9).

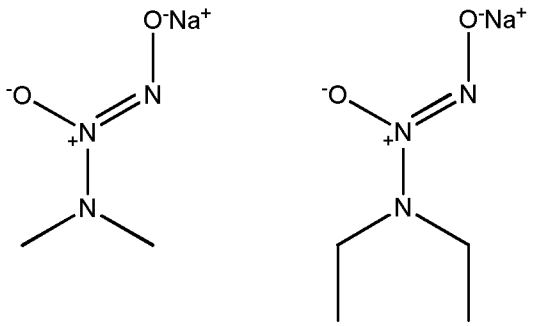
Solely to advance prosecution, applicants have deleted the terms "hydrate" and "solvate" from claim 1. The proposed amendments are believed to obviate this rejection.

Accordingly, applicants respectfully request withdrawal of this rejection.

VII. Claim Rejections - 35 U.S.C. § 102(b)

The Office has rejected claims 1, 15-16 and 43 as being anticipated by Fitzhugh *et al.*, "Qualititative Thin-Layer and High-Performance Liquid Chromatographic Analysis of 1-Substituted Diazen-1-ium-1,2-diolates on Aminopropyl Bonded Silica Gel", *Analytical Biochemistry* 301, 97-102 (2002). The Office action states:

"Compounds specifically taught [in Fitzhugh *et al.*] include:



1 and 2

(p. 99, Fig. 2)." Office action, pages 13-14.

Solely to advance prosecution, applicants have amended claim 1 to limit R^1 and R^2 to alkyl substituted with 1-4 groups that are halo or haloalkyl. The proposed amendments are believed to obviate this rejection.

Accordingly, applicants respectfully request withdrawal of this rejection.

VIII. Claim Rejections - 35 U.S.C. § 103(a)

The Office has rejected claims 1, 14-15 and 43 as being unpatentable over Fitzhugh *et al.* in view of Patani *et al.*, "Bioisosterism: A Rational Approach in Drug Design", *Chem. Rev.* 96, 3147-3176 (1996) and Ismail, "Important fluorinated drugs in experimental and clinical use", *J. Fluor. Chem.* 118, 27-33 (2002). The Office action states:

> It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute the terminal methyl hydrogens of the ethyl moieties of compound 2 taught by Fitzhugh, with fluorine atoms to give trifluoromethyl moieties, where the R groups of the diazeniumdiolate compound corresponds to $-CH_2CF_3$, i.e., the instant elected compound. The motivation would have been the expectation of increased lipophilicity enhancing absorption and/or improved translocation across membranes to a target location.

(Office action, pages 16-17). Applicants respectfully traverse this rejection.

The evidence and arguments of record fail to establish a *prima facie* case of obviousness. A "prima facie case depends on whether the prior art provided a suggestion or reason to choose a specific lead compound for modification, or to make the specific modification of the compound at issue." *Sanofi-Synthelabo v. Apotex*, 550 F.3d 1075 (Fed. Cir. 2008); *cert. petition filed*, 78 USLW 3065 (Jul 24, 2009)(citation omitted)(finding that a salt form of a separated stereoisomer was unobvious over the prior art racemate). The evidence and arguments of record provide no suggestion or reason for a person of ordinary skill in the art to select the specific "lead compound" and the specific structural modifications that would be necessary to make applicants' claimed compounds.

The Office action cites Fitzhugh *et al.* for its disclosure of diazeniumdiolates and, specifically, compound 2. While Fitzhugh *et al.* mentions the use of diazeniumdiolates as nitric oxide (NO) donors, the article focuses on high-performance liquid (HPLC) and thin-layer chromatographic (TLC) methods for detecting and quantifying diazeniumdiolates. Nowhere

does Fitzhugh *et al.* suggests that compound 2 is a particularly effective NO donor as compared to all other known NO donors, including the remaining compounds disclosed in Fitzhugh *et al.* Thus, the cited art offers no suggestion or reason for an ordinarily skilled artisan to consider any of Fitzhugh *et al.*'s compounds, let alone compound 2, as a starting point for developing new NO donors.

Even assuming that the cited art suggests the use of Fitzhugh *et al.*'s compound 2 as a lead compound, it does not suggest the specific structural modifications that would be needed to make applicants' claimed compounds. "[I]n cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new chemical compound." *Procter & Gamble Co. v. Teva Pharmaceuticals USA Inc.*, 556 F.3d 989, 994 (Fed. Cir. 2009); *Eisai Co. v. Dr. Reddy's Laboratories, Ltd.*, 553 F.3d 1353, 1358 (Fed. Cir. 2008); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007).

The Office action states that Patani *et al.* "provides motivation to substitute F for H in an active compound" while Ismail "provides motivation to utilize trifluoromethyl groups in active compounds." Office action, page 16. Absent hindsight reconstruction, such motivation is not evident.

Patani *et al.* discloses a multitude of bioisosteres: monovalent groups (e.g., fluorine, hydroxyl, amino, methyl, chloro, bromo, thiol), divalent groups (e.g., -O-, -S-, -CH_2-, -NH-), trivalent groups (e.g., -CH=), tetravalent groups (e.g., tert-butyl, trimethylsilyl, trimethylgermyl), ring equivalents (e.g., -NH-, -CH_2-, -S-, -Se-, -O-, -CH-, -N-), cyclic or non-cyclic non-classical replacements and non-classical replacements of functional groups (e.g., hydroxyl, carbonyl, carboxylate, amide, thiourea, halogen). Despite disclosing a broad and diverse range of bioisosteres, Patani *et al.* concedes that "no attempt was made to be exhaustive…" First paragraph, page 3148. Moreover, bioisosterism represents only "one approach used by the medicinal chemist for the rational modification of lead compounds..." Paragraph bridging pages 3147 and 3148. In view of the many tools for rational drug design and the immeasurable types

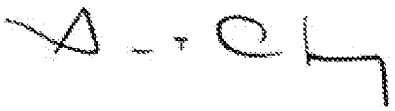
of bioisosteres, it is unclear how an ordinarily skilled artisan would have singled out fluorine replacement as the sole means for modifying Fitzhugh *et al.*'s compounds.

Ismail fails to overcome the deficiencies of Patani *et al.* Ismail discloses that, while fluorine may impart desirable characteristics to drugs, it may also produce undesirable effects: the bioisosteric replacement with fluorine can lead to "loss of potency" (second paragraph, page 30), and the introduction of a trifluorinated methyl group can either decrease biological activity (third paragraph, page 29) or cause adverse reactions (fourth paragraph, page 29). Thus, the cited art fails to provide any suggestion or reason to modify any one of Fitzhugh *et al.*'s compounds in the precise manner that would be necessary to produce applicants' claimed compounds.

Based on at least the foregoing reasons, applicants respectfully request withdrawal of this rejection.

Should the Examiner have any questions regarding this application, he is encouraged to contact applicants' undersigned representative at (202) 942-5000.

Respectfully submitted,



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